# Cytomegalovirus Complicating Inflammatory Bowel Disease: A 10-Year Experience in a Community-Based, University-Affiliated Hospital

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**Abstract:** There is an ongoing debate regarding the significance of cytomegalovirus (CMV) in colonic biopsies and the effect of antiviral therapy in patients with inflammatory bowel disease (IBD). In order to evaluate the possible impact of CMV disease on IBD patients, we reviewed charts of patients admitted through the emergency department with diagnoses of IBD and CMV over a 10-year period (January 2000 to November 2009). Laboratory test results and pharmacology databases were scrutinized, and pathology slides were re-evaluated when possible. The control group consisted of a historical group of IBD patients with flares who had been similarly evaluated in the emergency department but who did not have a diagnosis of CMV. Both chi-square tests and the student's *t*-test were used for analysis. The study consisted of 31 patients with IBD and CMV (median age, 60 years; 65% male; 58% ulcerative colitis patients). Immunohistochemistry confirmed the diagnosis in 19 cases (61%). Nine patients with CMV and IBD underwent a colectomy (29%) compared to 65 of the 581 patients in the control group (11.2%), who were evaluated during the same time period but did not have CMV ($P=.007$). Mortality was similar in both groups. Of the patients with CMV, 11 received ganciclovir. No significant differences in outcomes were noted with antiviral therapy. Although CMV disease is relatively uncommon in IBD patients, its presence may designate an increased risk for colectomy for reasons that are not yet clear. Patient outcomes may be independently affected by age and comorbidities. Systematic prospective studies could help determine the true effects of CMV on IBD patients.

Keywords
Inflammatory bowel disease, cytomegalovirus, clinical outcome, antiviral therapy

Cytomegalovirus (CMV) is a member of the Herpesviridae family of DNA viruses that is reported to affect between 40% and 100% of the general population. Acute infection or reactivation of CMV can occur, and the virus affects immunocompromised patients (eg, AIDS or transplant patients) more frequently than immunocompetent patients.[1]

There have been reports of CMV complicating steroid-resistant ulcerative colitis (UC); such complications have been reported less frequently in Crohn's disease (CD) patients.[2-7] Since the first publications on the topic, there has been debate regarding the clinical relevance of CMV infection in patients with inflammatory bowel disease (IBD). CMV has been implicated in increasing interleukin-6 production, and CMV cytotoxic autoantibodies have been detected in more than 50% of patients with either UC or CD.[8,9] However, the impact of CMV on IBD patients in terms of clinical outcome is still unclear, as some reports describe adverse outcomes, while other reports suggest only a bystander effect.[1,7,10-13]

The detection of CMV in serum levels (as opposed to tissue) divides CMV acquisition into 2 entities. Exclusive serologic detection suggests CMV infection, whereas tissue detection is considered to be indicative of CMV disease.[1] A meta-analysis of CMV complicating IBD conducted by Hommes and associates hypothesized that diagnostic outcomes could be divided into 3 stages: Stage 1 ("initiation") is associated with positive immunoglobulin (Ig)G serology test results, stage 2 ("reactivation") is associated with both positive serology test results and identification of CMV in tissue; and stage 3 ("consolidation") is associated with positive serology, tissue identification, and positive polymerase chain reaction (PCR) test results.[7]

As a result of CMV's pathogenic uncertainty in IBD, the role of antiviral treatment is also unclear. Unfortunately, to date, there have not been any controlled trials of antiviral therapy to clarify this issue. We report a retrospective analysis of patients with CMV disease (diagnosed by tissue) superimposed on an IBD flare who required hospitalization at Sir Mortimer B. Davis Jewish General Hospital in Montreal, Quebec during a 10-year period. The aims of this analysis were to evaluate outcomes (colectomy, death, or discharge) in a cohort of patients who had been diagnosed with CMV and to determine whether antiviral treatment impacted these outcomes. A historical group of patients admitted in the same time frame for IBD flares in whom CMV was not identified was also evaluated for the same parameters.

## Methods

### *Inclusion of Patients with Cytomegalovirus and Inflammatory Bowel Disease*

The diagnosis of both IBD and CMV in a patient was based on initial identification of the International Classification of Diseases (ICD) code from the Sir Mortimer B. Davis Jewish General Hospital's patient database. The Department of Gastroenterology's database includes patients treated in the emergency room and hospitalized patients but not patients who were seen only in a clinic or doctor's office. Identified cases were then searched for the presence of tissue diagnosis through the Department of Pathology. Whenever possible, the tissue was recut and stained using immunohistochemistry (IHC) methods for verification. In addition, an existing laboratory database was searched for ancillary serologic diagnoses. Therefore, all included CMV cases were identified twice (by ICD code and pathology); no cases were included based on serology alone.

### *Chart Review*

Chart review consisted of patients admitted through the emergency department with diagnostic codes for IBD and CMV (for CD: ICD-9, 555.1, 555.2, 555.9; ICD-10, K50.1–K50.9; for UC: ICD-9, 556.9; ICD-10, K51.0–K51.9; and for CMV: ICD-9, 078.5; ICD-10, B25.9). Procedural codes for surgery were also included from January 2000 to November 2009 for verification and were reviewed under the auspices of the Medical Records Department with the approval of the Ethics Committee of the institution. No patients were contacted.

Abstracted demographic data included age; sex; IBD type, site, and duration; treatments (surgical or medical) prior to and during hospitalization; administration of antiviral agents; surgical intervention (colectomy at current admission); and death. In addition, white blood cell counts and levels of hemoglobin and albumin were tabulated. All patients were evaluated for IBD flare, although it was not possible to use a formal disease activity index. We accepted the patient's history, physician's judgment, and laboratory values as indicators of the severity of the IBD attack. Therefore, outcome measures were colectomy (failure of medical treatment), death, or hospital discharge (a surrogate assessment of improved outcome). No attempt was made to ascertain patient follow-up after discharge. Diagnostic differentials between UC and CD were based on patient history, including radiology, endoscopy, and pathology findings.[14]

### *Review of Hospital Databases*

The hospital laboratory database was searched for CMV serology and/or blood PCR results. The pharmacology database was scrutinized for use of ganciclovir or other antiviral agents using identifiers from the cohort. Other recorded information included dosage, duration of use, and whether immunomodulators were continued or stopped. This database was established in the middle of 2005.

### *Tissue Review*

Pathology records of the cohort were reviewed. When available, tissue blocks were recut, stained with hematoxylin and eosin (H&E), and analyzed via IHC to confirm the presence of the CMV early antigen. These blocks had been stored from the time of the original biopsy or tissue sample collection.

The H&E-stained slides were used to confirm the presence of IBD and to evaluate the presence of viral cytopathic effects and ulcerations. Paraffin samples of colonic tissue were obtained from the Department of Pathology with approval as above. Tissue samples were cut into 4-µm pieces, placed on SuperFrost/Plus slides (Fisher), and dried overnight at 37°C. The slides were then loaded onto the Discovery XT autostainer (Ventana Medical System). Immunostaining for CMV was performed online using a heat protocol. A mouse monoclonal anti–human CMV antibody (clone CCH2 and DDG9; Dako) that had been diluted 1:50 in antibody diluents solution was manually applied to the slides for 32 minutes, followed by the appropriate detection kit (OmniMap anti–mouse HRP). A negative control was performed by repeating the process with the omission of the primary antibody. Slides were counterstained with hematoxylin for 4 minutes, blued with bluing reagent for another 4 minutes, removed from the autostainer, washed in warm soapy water, dehydrated through graded alcohols, cleared in xylene, and mounted with permount. Sections were analyzed via conventional light microscopy.

The immunostained slides were evaluated for the presence of nuclear staining for the CMV early antigen, sometimes accompanied by cytoplasmic staining. The type of cell infected (endothelial, fibroblast, or epithelial) was recorded, as was the presence of CMV-positive cells in the granulation tissue from the ulcer (when applicable). The number of CMV-positive cells was expressed using a semiquantitative grading scale ranging from 1 to 3 (1=rare, 2=common and easy to find, and 3=numerous cells positive for CMV). The pathologist was blinded to the treatments received by the patients.

### *Historical Control Group*

A historical control group with diagnostic codes for IBD (CD or UC) was also identified from emergency visits during the same period of time. Patients were excluded if they were elective admissions (eg, from obstetrics) or if they had undergone an elective IBD operation (such as colectomy for dysplasia or staged pouch construction after failing medical therapy); also excluded was a cohort of 146 patients who had been admitted with CD and suspected small bowel obstruction. For the remaining patients in the historical control group, the following information was recorded: sex, age, number and length of hospitalizations, IBD type and site, comorbidities, average age, death, and need for colectomy. Patients' charts were not reviewed for further details.

### *Statistical Analysis*

Because of the nature of the patient groups, statistical analysis was performed to compare IBD patients with CMV versus IBD patients without CMV. When possible, chi-square tests with Fisher exact correction were used to compare fixed variables between these groups. An unpaired *t*-test was used to compare normally distributed, continuous variables. Calculations were performed at the Statpages.org website. All *P*-values were 2-tailed, and statistical significance was set at $P<.05$.

## Results

### *Patients with Cytomegalovirus and Inflammatory Bowel Disease*

Thirty-five cases were found in the medical archives, but 4 cases were excluded. In 2 of the excluded cases, CMV could not be confirmed on re-evaluation (1 based on pathology and the other based on a review of the patient's records). The other 2 excluded cases did not have IBD. Thus, 31 patients remained for analysis.

Demographics of the 31 patients are outlined in Table 1. Thirty patients presented with IBD exacerbation with increased diarrhea, abdominal pain, and/or rectal bleeding. Of the 31 cases evaluated in the emergency department, 9 cases were discharged due to improvement within 24–72 hours, and 22 cases were hospitalized for longer periods of time. The mean age of the entire group was 57.9 years (median, 60 years; range, 19–84 years), 20 patients (65%) were male, 18 patients (58%) had UC, and 13 patients (42%) had CD. Surgical IBD treatment prior to admission was uncommon. Only 1 patient (an 81-year-old woman) had had colon cancer in an area of CD resection. Immunomodulators used by the patients ranged from prednisone to biologic agents (with 1 patient receiving infliximab [Remicade, Janssen Biotech]) in 25 of the patients (81%) prior to the current hospitalization.

In addition, 15 of the 31 patients (48%) had comorbidities, which included 6 patients with renal disease and elevated serum creatinine levels (1 of whom underwent renal transplantation), 3 patients with heart failure, 3 patients with hypertension, 2 patients with remote colon or rectal cancer that had previously been treated with chemotherapy, 2 patients with diabetes mellitus type 2, 1 patient with polymyositis, 1 patient with remote breast cancer, 1 patient with remote bladder cancer, 1 patient with asthma, and 1 patient who had received levothyroxine sodium (Synthroid, Abbott) for hypothyroidism. A subanalysis of patients showed that more comorbidities occurred in CD patients than UC patients (11/13 [85%] vs 4/18 [22%]; $P=.001$). In addition, patients with CD were older (64.0±17.5 years vs UC, 53.2±18.7 years; $P=.11$). The between-group difference in disease duration from initial diagnosis was also insignificant (CD, 7.83±6.42 years vs UC, 9.01±6.33 years; $P=.6$).

Review of the hospital laboratory system disclosed only 4 patients with positive CMV serology test results, 3 of whom also had positive blood PCR test results. Only

**Table 1.** Demographics of Study Patients with Inflammatory Bowel Disease Complicated by Cytomegalovirus Disease

| Patient # | Disease | Age (yrs) | Sex | Disease duration (months) | Disease site | Treatment | Albumin level (g/L) | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | UC | 59 | F | 12 | Left colon | Prednisone | 28 | Discharge |
| 2 | UC | 33 | M | 84 | Left colon | Prednisone, cyclosporine A | 35 | Discharge |
| 3 | UC | 19 | M | 24 | Pancolon | Prednisone, infliximab | 29 | Colectomy |
| 4 | CD | 81 | F | 120 | Ileocolon | Prednisone | 13 | Discharge |
| 5 | CD | 71 | F | 60 | Ileocolon | Azathioprine | 22 | Discharge |
| 6 | UC | 51 | M | 36 | Pancolon | Prednisone | 28 | Colectomy |
| 7 | CD | 65 | F | 12 | Left colon | Prednisone | 28 | Discharge |
| 8 | UC | 55 | F | 108 | Left colon | Prednisone, azathioprine | 40 | Discharge |
| 9 | UC | 61 | M | 60 | Pancolon | Prednisone | 12 | Colectomy |
| 10 | UC | 35 | F | 120 | Pancolon | 6-mercaptopurine | 39 | Discharge |
| 11 | CD | 41 | M | 156 | Right colon | Prednisone | 24 | Death* |
| 12 | UC | 84 | M | 180 | Left colon | Prednisone | 37 | Discharge |
| 13 | CD | 68 | M | 84 | Ileocolon | Prednisone | 45 | Discharge |
| 14 | UC | 36 | F | 48 | Left colon | Prednisone | 46 | Discharge |
| 15 | CD | 78 | M | 84 | Right colon | Prednisone, 5-aminosalicylic acid | 39 | Discharge |
| 16 | CD | 43 | F | 12 | Pancolon | Prednisone, 5-aminosalicylic acid | 29 | Discharge |
| 17 | UC | 35 | F | 2 | Pancolon | Methotrexate | 45 | Discharge |
| 18 | CD | 35 | M | 36 | Right colon | Prednisone, 5-aminosalicylic acid | 38 | Discharge |
| 19 | UC | 78 | M | 144 | Left colon | Prednisone, 5-aminosalicylic acid | 22 | Discharge |
| 20 | CD | 79 | M | 24 | Pancolon | Prednisone | 28 | Discharge |
| 21 | CD | 40 | M | 48 | Right colon | Prednisone | 33 | Discharge |
| 22 | UC | 55 | M | 24 | Pancolon | Prednisone, methotrexate | 38 | Discharge |
| 23 | UC | 37 | M | 144 | Left colon | Prednisone, 6-mercaptopurine | 42 | Discharge |
| 24 | UC | 76 | F | 24 | Left colon | Prednisone, 5-aminosalicylic acid | 23 | Discharge |
| 25 | UC | 78 | F | 264 | Left colon | Prednisone, 5-aminosalicylic acid | 29 | Discharge |
| 26 | UC | 67 | M | 180 | Pancolon | Prednisone | 29 | Colectomy |
| 27 | CD | 76 | M | 120 | Right colon, left colon | Prednisone | 25 | Colectomy |
| 28 | UC | 42 | M | 24 | Pancolon | Prednisone | 25 | Colectomy |
| 29 | CD | 79 | M | 300 | Ileocolon | Prednisone | 20 | Colectomy |
| 30 | UC | 57 | M | 120 | Pancolon | Prednisone, cyclosporine A | 44 | Colectomy |
| 31 | CD | 76 | M | 12 | Ileocolon | Prednisone | 22 | Colectomy |

Patients are listed according to whether they were treated with ganciclovir (patients 1–11) or were not (patients 12–31). Patients who were not treated with ganciclovir are then listed according to precolectomy or postcolectomy diagnosis of cytomegalovirus in tissue (patients 26–31).

*Complicated by renal failure and transplantation more than 2 years prior to hospitalization.

CD=Crohn's disease; F=female; M=male; UC=ulcerative colitis.

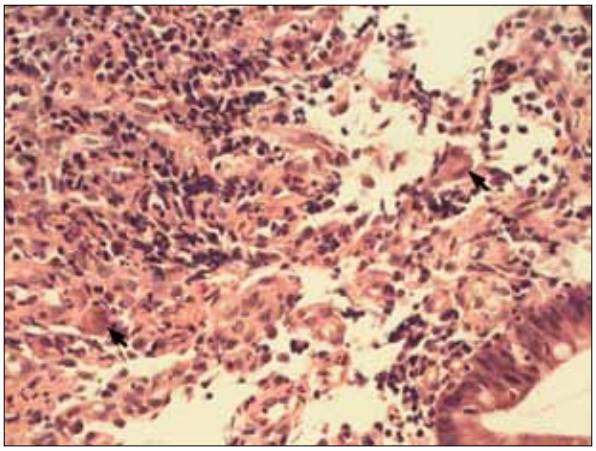

**Figure 1.** Cytopathic effects of cytomegalovirus (arrows) in a fibroblast cell (hematoxylin and eosin stain, 400× magnification).

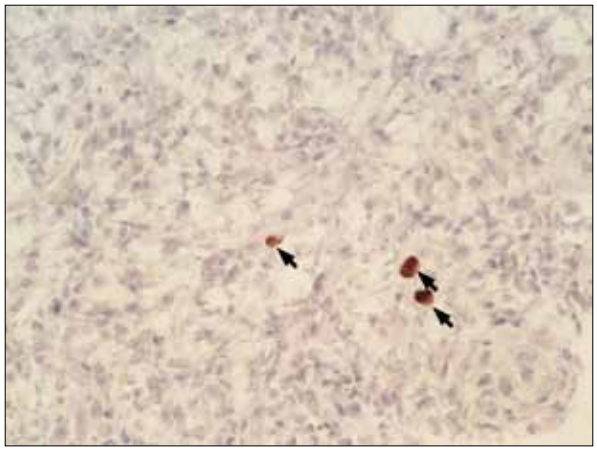

**Figure 2.** Immunohistochemistry of cytomegalovirus-infected cells (arrows; 400× magnification).

2 patients were positive for IgG. Results of the IgM and PCR tests were negative. Serology and PCR tests were underutilized and, as a result, did not contribute as an adjunct to diagnosis.

**Pathology** Tissue from 25 cases was retrieved for pathologic review, and 19 cases underwent IHC (13 cases in the context of the study). Thus, a total of 19 cases were confirmed to have tissue evidence of CMV (19/31; 61.3%). Examples of cytopathic effects of CMV and IHC enhancement are shown in Figures 1 and 2. In the remaining 6 of the 25 cases, storage deterioration rendered the specimens unamenable to IHC analysis. In these cases, the original interpretation was accepted as consistent with CMV disease.

Table 2 lists patients with verified pathology results, their outcomes, grade of IHC (as defined in the Methods section), cell type associated with CMV, presence of cytopathic effects, and the association of the CMV yield with the ulcer base. The ulcer base site was positive for CMV in 19 of the 25 cases (76%). Comparison of the yield of cytopathic effects to the yield of IHC (in the 19 cases) demonstrated that IHC was more sensitive (10/19 vs 19/19; $P$=.004).

**Patient Outcomes** In the CMV group, 9 patients (29%; all males) had undergone a colectomy. In 6 of these cases, the presence of CMV was discovered only after surgery. Their mean age (64 years) was a little older than that of the entire group of IBD patients with CMV. Three of these latter cases had UC, and 3 cases had CD. Five of the cases occurred at the beginning of the decade under study, and 1 patient underwent surgery in 2007. The presence of CMV was not sought preoperatively in these 6 patients for reasons that are not clear, but the diagnosis may not have been considered. Only 1 death (3.2%) was reported. This patient had also undergone a failed renal transplantation and had experienced several episodes of upper gastrointestinal bleeding. The rest of the patients were eventually discharged.

All 31 patients received immunosuppressants, and only 3 patients were not receiving corticosteroids. Six of the 28 patients were on combined immunosuppressants or biologic agents. A formal assessment of steroid resistance (>7 days on intravenous [IV] corticosteroids) could not be ascertained due to lack of sufficient documentation in the pharmacology database.

Antiviral therapy was used in 11/31 patients (35.5%). No therapy was undertaken in the majority of patients who were rapidly discharged (9 patients) or in the 6 patients in whom the presence of CMV was discovered after colectomy. In the remaining 5 patients, it was unclear why treatment was not initiated (although these patients may have been less ill). Of the 11 patients, 10 were treated with IV ganciclovir (5 mg/kg/day) and 1 with oral ganciclovir (1 g twice daily [BID]). Only 5 cases could be verified because of inclusion in the database, which was started in 2005. The average duration of therapy for these 5 patients was 15.8 days (range, 8–28 days). In 3 cases, immunomodulators were abruptly stopped, and in 2 cases, treatment was slowly tapered. One additional case was treated with oral ganciclovir (1 g by mouth [PO] BID) as an outpatient in 2007 and did not appear in the in-hospital database. This patient was later treated again with oral valganciclovir at the same dose. The other patients were treated before 2005 and were not identified in the hospital database.

The demographics and outcomes of patients treated with antiviral medications compared to those who were not treated with antiviral medications are shown in

**Table 2.** Characteristics of Cytomegalovirus Cases (N=25) Confirmed and Unconfirmed by Histopathology (According to Immunohistochemistry [IHC] Grades When Possible)

| Patient characteristics | IHC grade* | Cell type | Cytopathic effects | Ulceration or erosion |
|---|---|---|---|---|
| **Confirmed cases of cytomegalovirus** | | | | |
| 55 yrs old, female, ulcerative colitis, discharged | 1 | Endothelial | – | + |
| 43 yrs old, female, Crohn's disease, discharged | 1 | Fibroblast | – | + |
| 35 yrs old, female, ulcerative colitis, discharged | 1 | Fibroblast | – | + |
| 65 yrs old, female, Crohn's disease, discharged | 2 | Fibroblast** | – | + |
| 81 yrs old, female, Crohn's disease, discharged | 2 | Endothelial, fibroblast, epithelial | – | – |
| 51 yrs old, male, ulcerative colitis, colectomy | 2 | Fibroblast, endothelial** | + | + |
| 19 yrs old, male, ulcerative colitis, colectomy | 1 | Fibroblast, endothelial | – | – |
| 78 yrs old, male, Crohn's disease, discharged | 2 | Fibroblast** | + | + |
| 36 yrs old, female, ulcerative colitis, discharged | 1 | Fibroblast** | – | + |
| 33 yrs old, male, ulcerative colitis, discharged† | 2 | Unclear | – | + |
| 59 yrs old, female, ulcerative colitis, discharged | 1 | Endothelial** | – | + |
| 68 yrs old, male, Crohn's disease, discharged | 1 | Endothelial** | + | – |
| 78 yrs old, male, ulcerative colitis, discharged | 1 | Endothelial** | + | + |
| 42 yrs old, male, ulcerative colitis, colectomy | 1 | Fibroblast** | + | + |
| 76 yrs old, male, Crohn's disease, colectomy | 2 | Endothelial** | + | + |
| 57 yrs old, male, ulcerative colitis, colectomy | 3 | Endothelial, fibroblast, epithelial** | + | + |
| 55 yrs old, male, ulcerative colitis, discharged | 1 | Endothelial, fibroblast** | + | + |
| 35 yrs old, male, Crohn's disease, discharged | 2 | Endothelial** | + | + |
| 76 yrs old, male, Crohn's disease, colectomy | 1 | Endothelial** | + | + |
| **Unconfirmed cases of cytomegalovirus‡** | | | | |
| 84 yrs old, male, ulcerative colitis, discharged | Not done | Endothelial | + | – |
| 40 yrs old, male, Crohn's disease, discharged | Not done | Endothelial | + | + |
| 78 yrs old, female, ulcerative colitis, discharged | Not done | Endothelial | + | – |
| 79 yrs old, male, Crohn's disease, colectomy | Not done | Fibroblast | Unclear | Unclear |
| 37 yrs old, male, ulcerative colitis, discharged | Not done | Unclear | Unclear | + |
| 61 yrs old, male, ulcerative colitis, colectomy | Not done | Unclear | Unclear | + |

The 6 patients with cytomegalovirus not listed in this table had a diagnosis of cytomegalovirus based on the original pathology report, but this diagnosis was not confirmed by IHC.

*1=rare; 2=common and easy to find; 3=numerous cells positive for cytomegalovirus.
**Cytomegalovirus was found within granulation tissue of the ulcer bed.
†This patient's histopathology and IHC findings were confirmed via re-evaluation of his original slides, as no block was available for restaining.
‡These cases were originally classified as having inflammatory bowel disease complicated by cytomegalovirus, but it was not possible to confirm their diagnosis upon re-evaluation of the original slides.

**Table 3.** Comparison of Patients with Cytomegalovirus (CMV) Disease Who Were Treated with Ganciclovir and Those Who Were Not Treated with Ganciclovir

| | Median age, yrs | Sex, F/M | Mean duration of IBD, months (SD) | Mean hgb level, g/L (SD) | Mean WBC, $10^9$/L (SD) | Mean albumin level, g/L (SD) | # of patients who underwent colectomy | IHC grade** |
|---|---|---|---|---|---|---|---|---|
| Patients treated with ganciclovir* (N=11) | 55 | 6/5 | 72 (49.2) | 102 (18.1) | 11.2 (5.7) | 27.1 (9.2) | 3/11 | 3/6 |
| Patients not treated with ganciclovir (N=20) | 67.5 | 5/15 | 93.7 (86.4) | 112 (23.8) | 9.3 (7.6) | 33 (8.8) | 6/20 | 5/13 |

The decision to use ganciclovir was determined by the severity of the attack, whether CMV was recognized prior to surgery, and the length of hospitalization (emergency stay <3 days compared to a longer stay). In 5 patients, the treatment decision could not be verified. Normal laboratory test values are a hemoglobin (hgb) level of 120–152 g/L for women and 140–175 g/L for men, a white blood cell count (WBC) of 4.0–11.0 × $10^9$/L, and an albumin level of 35–51 g/L.

*1 patient died of multiple problems.
**The IHC grade comparison was made using the cellular frequency semiquantitative grade (1–3) from Table 2. The numerator represents the stain grade >1. A higher intensity of stain signifies a more positive frequency of CMV cells.

F=female; IBD=inflammatory bowel disease; IHC=immunohistochemistry; M=male; SD=standard deviation.

Table 3. The only clinical difference between the groups was that the ganciclovir-treated patients had lower albumin levels (ganciclovir-treated patients, 27.1±9.2 g/L vs ganciclovir-untreated patients, 33±8.8 g/L; normal, 35–51 g/L). The mean albumin level of the colectomized, ganciclovir-untreated group was similar to that of the entire ganciclovir-treated group (26.1±3.3 g/L). Furthermore, the grade of IHC in the 19 pathology-verified patients did not correlate with the risk of colectomy (*P*=.34).

### *Patients with Inflammatory Bowel Disease without Cytomegalovirus*

To compare the outcomes of IBD patients with and without CMV infection, we retrieved data from 917 emergency IBD admissions during the study period. After excluding cases that did not meet predefined criteria, 581 patients (CD, 370 [64%]; UC, 211 [36%]) remained for analysis. The mean age of patients in this non-CMV group was 49.4 years, and 56.7% were female. There were 65 emergency colectomies (11.2%) within the study period in this group. Comparison of this group with the group that had CMV and IBD is shown in Table 4.

The current study revealed a very crude prevalence of diagnostically recognized CMV disease in IBD patients (31/612 or 5% during the decade [0.5% per year]). There were a total of 74 emergency colectomies in the entire study population (CMV and non-CMV groups combined), translating into a colectomy rate of 12.1%, with a mean patient age of 51.2 years. There were a total of 16 deaths in the combined groups. The rate of colectomy was higher in the CMV-recognized group (9/31, 29%) compared to the non-CMV group (65/581, 11.2%; *P*=.007). Significance was retained even if only the 19 pathology-verified cases were included (6/19; *P*=.017). Of the 9 colectomized patients, 6/18 had UC (33%), and 3/13 had CD (23%; *P*=.8). Moreover, all of the colectomies in the CMV group occurred in men. Of the colectomies in the non-CMV group, 25 (11.8%) occurred in UC patients, and 40 colon surgeries (10.8%) were performed in patients with CD (*P*=.7). More than half (55%) of colon resections in this group occurred in women. Rates of death were not significantly different between the 2 groups (*P*=.55).

Since a large percentage of CD cases were found to be affected by CMV in the current study, we compared rates of CMV within CD and UC admissions. Based on exposure, the rates of CMV in CD cases versus UC cases were 3.5% (13/370) versus 8.5% (18/211; *P*=.012). Thus, proportionately more UC patients than CD patients (2.4-fold) were affected with CMV.

## Discussion

This retrospective evaluation of CMV disease coexisting with IBD represents one of the longest and largest experiences published to date. This study is based on the population of a community-based, university-affiliated hospital and, as such, could represent a more general experience. The 5 main observations from this study were: Although immunomodulator-treated CD patients were affected, UC patients were at greater risk for CMV disease; older age and comorbidities may have contributed to the risk

**Table 4.** Comparison of Characteristics in Inflammatory Bowel Disease (IBD) Patients with Cytomegalovirus (CMV) Versus IBD Patients without CMV

| Characteristic | IBD with CMV (N=31) | IBD without CMV (N=581) |
|---|---|---|
| Female (%) | 11 (35.5) | 329 (56.7) |
| Average age, yrs | 57.9 | 49.4 |
| Median age, yrs | 60 | 45 |
| Range of ages, yrs | 19–84 | 17–97 |
| Crohn's disease (%) | 13 (42) | 370 (64) |
| Only in the colon (%) | 8 (61.5) | 128 (35.8) |
| In the colon and small bowel (%) | 5 (38.5) | 67 (18.5) |
| Unclassified (%) | 0 (0) | 225 (38.7) |
| Ulcerative colitis (%) | 18 (58) | 211 (36) |
| Total comorbidities (%)* | 15 (48) | 225 (38.7) |
| Hypertension (%) | (20) | (58) |
| Metabolic disease (%) | (20) | (24.5) |
| Heart disease (%) | (20) | (49.7) |
| Renal disease (%) | (40) | (25.8) |
| Chronic lung disease or asthma (%) | (6.6) | (25.8) |
| Autoimmune disease (%) | (6.6) | (3.4) |
| Average number of hospitalizations | 3.3 | 1.73 |
| Average length of hospital stay, days | 25.2 | 10.5 |
| Total colon resections (%)** | 9 (29) | 65 (11.2) |
| Colon resections in ulcerative colitis patients (%)† | 6 (33) | 25 (11.8) |
| Colon resections in Crohn's disease patients (%) | 3 (23) | 40 (10.8) |
| Total deaths (%)‡ | 1 (3.2) | 15 (2.6) |

*The percentages do not total 100% because some patients had multiple comorbidities.
**The difference between IBD patients with CMV and IBD patients without CMV was $P$=.007 (inclusion of only patients with CMV documented by immunohistochemistry, $P$=.017).
†Comparisons of colon resection frequencies between ulcerative colitis and Crohn's disease within each group were not significant.
‡Comparison of mortality rates between the 2 groups were not significant.

of CMV in both CD and UC patients; the presence of tissue-recognized CMV may have increased the risk or portended a higher risk for colectomy; the use of antiviral agents in the study did not appear to reduce the need for surgery; and biopsies of the ulcer base that were tested with IHC may have increased the diagnostic yield.

This study revealed a very crude prevalence rate of 0.5% per year for tissue-recognized CMV affecting IBD. In general, CMV-positive tissue is found more frequently in IBD patients than in healthy controls.[15] Patients with CD are less commonly affected than those with UC, and CMV has been identified in 10–40% of tissue in UC patients.[15-17] However, serologic distribution is similar in UC and CD patients.[9] In a meta-analysis of 9 case series reported prior to 2004, 19.5% of patients affected by CMV had CD.[7] Forty-two percent of the patients in the current study were coded as having CD, making this experience one of the largest reported. However, subanalysis revealed that UC patients were affected 2.4 times more frequently than CD patients. Therefore, the higher CD contribution reflected the higher number of CD patients seen in the emergency department during the study period.

Typically, immune-suppressed IBD patients are at the highest risk for CMV disease.[2-4] In a study of patients with severe UC who were treated with steroids, Daperno and associates reported steroid resistance (no response in 7 days) in 43% of patients.[18] Of these, 24% had no response (within 7 days, as defined by the group). In this select group of resistant patients, 37% underwent colectomy, but only 1 patient was found to harbor CMV, suggesting that treatment resistance was the primary factor for the need for surgery.[18] In the current study, although all patients with both CMV and IBD received immunosuppressive agents and 90% were taking corticosteroids, we were unable to formally assess steroid (or other therapeutic) resistance. However, we surmise from the long period of hospitalizations (>25 days) that many of the admitted patients did not respond quickly to medical therapy. We were also unable to verify equivalent or lower rates of steroid resistance in the historical group of IBD patients without CMV.

Several other parameters may also contribute to a higher risk of CMV disease. Male gender appeared to be more common in CMV patients. The relatively high number of patients with CMV and CD may be due to their older age and higher frequency of comorbidities. In an earlier meta-analysis of CMV colitis in nontraditionally immunocompromised patients, we noted that patients over 55 years of age were more likely to have comorbidities.[19] There were also more males with worse outcomes. It is of note that age and comorbidities were also found to predispose IBD patients to bacterial hospital-acquired infections.[20] These observations offer additional explanations for the noted distribution and outcomes. Alternatively, a more severe disease course was suggested in younger patients with IBD who did not have CMV.[21,22]

The benefit of using antiviral medication in patients with CMV disease is controversial, possibly reflecting

the debate regarding CMV's pathogenic role. Several papers have reported advantages with antiviral treatment and overall improvement in severe cases after immunomodulator therapy is stopped.[6,23-25] However, other papers have reported less favorable outcomes regarding the need for colectomy despite clearance of CMV.[13,26] In our experience, the use of ganciclovir was not associated with significant benefit. In the ganciclovir-treated group, 3 colectomies were performed, and 1 patient died. However, in the group that was not treated with ganciclovir, CMV was not recognized prior to colectomy, making it difficult to establish a fair comparison. Nevertheless, it is not uncommon to diagnose CMV in colonic specimens unexpectedly after surgery.[27] The only clinical difference between ganciclovir-treated and ganciclovir-untreated patients was a lower mean albumin level in the former group, but this was only of marginal statistical significance. The albumin level in 6 ganciclovir-untreated but colectomized patients was comparable to that of the ganciclovir-treated group, suggesting that patients requiring colectomy were sicker.[28]

An important issue involves the role that CMV plays in IBD patients. Does the presence of CMV make an IBD patient sicker (perhaps via increased therapeutic resistance), or is a sicker and therapy-resistant patient more likely to display CMV (as noted in other immunosuppressed states)? The current study does not allow for establishing pathogenic conclusions regarding the role of CMV in IBD outcomes. Similar distributions of comorbidities between the group with CMV and IBD and the non-CMV group could suggest that the appearance of CMV aggravated medical treatment response and worsened outcomes. However, the failure to find a histologic IHC dose response detracts from this notion. In addition, the failure to observe an impact of antiviral therapy on the need for colectomy tends to support CMV as a marker, rather than as a pathogenic agent. However, the number of treated patients was too small to establish firm conclusions.

A more structured diagnostic approach to CMV disease complicating IBD may help to distinguish the role played by the virus. The 3-stage approach suggested by Hommes and coworkers may be a useful tool.[7] Serology test results (both IgG and IgM) could help determine whether acute infection or reactivation of latent infection is present. However, it is less useful to detect acute infection in immunocompromised patients.[29] A blood or stool PCR test result could help diagnose the presence of CMV.[30] In addition, as noted above, judicious use of biopsy, particularly sampling of the ulcer base followed by staining with IHC, could increase the diagnostic yield.[31-33]

Weaknesses in the current study include those inherent to retrospective studies. In the target CMV cases, we were only able to verify approximately 40% from laboratory databases and 60% from pathologic material. Therefore, diagnostic data relied on codes and chart reviews with inherent inaccuracies. The control group data solely relied on medical record classification; thus, a very crude estimated prevalence rate of CMV in IBD patients was made. However, there should be fewer diagnostic errors in patients who underwent colectomy. The 6 patients who were colectomized in the untreated CMV group were diagnosed by careful pathologic assessment. This is usually applied to all cases of colectomy. Therefore, in the historical cohort, significant numbers of CMV were unlikely to have been missed. The role of steroid-refractoriness as a harbinger of CMV infection could not be assessed. It is known that this variable plays a role in CMV infections. However, we were unable to properly assess steroid use in the historical controls. It is likely that steroid resistance did play an important role, but the magnitude of this effect in patients diagnosed with CMV is unknown. Finally, because ganciclovir-treated patients were likely sicker than patients who had not been treated with ganciclovir, the failure of the drug to impact outcomes may have been biased. Despite these shortcomings, we think that the current study gives a realistic, unselected view of the impact of CMV complicating IBD in a large, community-based, university-affiliated hospital.

## Conclusion

The complication of CMV in IBD patients is a relatively uncommon occurrence. Older age, male gender, comorbidities (such as diabetes mellitus and renal failure), a low albumin level, and the presence of tissue-recognized CMV may be associated with an increased risk of the need for colectomy. However, the current observational study is unable to settle the controversy regarding the specific role of CMV in IBD patients. These variables need further prospective assessment. Although antiviral treatment did not appear to reduce the need for surgery in the current study, randomized controlled trials will be needed to assess any benefits.

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